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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/879,442	06/11/2001	Vincent Dubois	COUL-015/02US	3549

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EXAMINER	
KOSAR, ANDREW D	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/879,442	DUBOIS ET AL.	
	Examiner	Art Unit	
	Andrew D Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-32,37,38 and 118-120* is/are pending in the application.

4a) Of the above claim(s) *20,21,24 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-19,22,23,25-28,30-32,37,38 and 118-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/30/01,9/20/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 4, 33-36, and 39-117 have been cancelled by Applicant. Claims 118-120 have been added. Claims 1-3, 5-32, 37, 38, and 118-120 are pending.

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on August 26, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants election with traverse of the amino acid sequence SEQ ID NO:38 in the reply on August 26, 2004 is acknowledged. The traversal on the grounds that the restriction requirement among the amino acid sequences should be treated as an election of species requirement, with the search being extended to the nonelected sequences if the elected sequence is determined to be allowable. This is not found persuasive because no sequence would render the others obvious, and therefore each is patentably distinct. Accordingly, each sequence would require a separate search and would be undue burden on the examiner.

This requirement is still deemed proper and therefore made FINAL.

Applicants have elected SEQ ID NO:38 from claim 13. Because SEQ ID NO: 1-3 comprise the same amino acid sequence as SEQ ID NO:38, they are also deemed to be elected sequences, and have been searched and examined together with the elected sequence. Further, the Examiner has included SEQ ID NO: 17, 21, 22, 24, 28, and 31 with SEQ ID NO:38, because they share the core sequence βAla-Leu-Xaa-Leu,

wherein Xaa is a natural amino acid or unnatural amino acid with a normal peptide backbone (-NH-CHR-CO-) and are alleged to be cleavable by TOP. The Examiner's search of the sequence was conducted using the structure, and thereby excluding amino acids which do not share the 'normal' peptide backbone, such as Xaa= βAla.

The sequence has been searched as X-βAla-Leu-Ala-Leu-Dox and X-βAla-Leu-Xaa-Leu-Dox wherein X is a stabilizing group; as Suc-βAla-Leu-Ala-Leu-Y and Suc-βAla-Leu-Xaa-Leu-Y, wherein Y is a therapeutic agent; and as X-βAla-Leu-Ala-Leu-Y and X-βAla-Leu-Xaa-Leu-Y.

Examination on the merits has been conducted in view of the elected species. As such, claims 20, 21, 24, and 29 have been withdrawn from consideration by the Examiner as not reading upon the elected species. Claim 29, in particular requires that the peptide not be cleavable by CD10, however as shown by Pan, *et al.*[1] CD10 cleaves the species elected (p5526: last paragraph; and p5528: figure 2), and therefore cannot read upon the elected species.

Claims 1-3, 5-19, 22, 23, 25-28, 30-32, 37, 38, and 118-120 are examined on the merits.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 and 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the

[1] Pan, et al. Cancer Research. (2003) 63, 5526-5531.

specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Information Disclosure Statement

References F1, F2, F4, F7, and F14 have been considered insofar as they are either English equivalents of, or claim priority to, US Patents listed as P2-P4, P7, and P13 as stated by Applicant.

Examiner Notes

Herein, citations to relevant passages of U.S. Patents are as (Column #: line #), i.e.- (c3:1+). For foreign patents and non-patent literature it is as (Page #), i.e.- (p1), and when applicable (Page #: line or paragraph #), i.e.- (p1:4 or p1:p4).

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent 5,962,216[2] (the English equivalent of WO 96/05863[3], used herein as ´216).

In view of the elected species, the instant claims are drawn to a conjugate comprising βAla-Leu-Ala-Leu, conjugated to a therapeutic agent, doxorubicin.

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[2] PTO-1449 P13.
[3] PTO-1449 F15.

'216 teaches degradation of the tetrapeptide linked to doxorubicin (c12:29+, Example 3). The compound is inherently cleavable by TOP, as it is the same tetrapeptide as the elected species.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over '216, as applied *supra*, in view of Li, *et al.*[4], and DeJongh, *et al.*[5].

The instant claims are presented *supra*. The claims are drawn to the tetrapeptide succinylated.

'216 does not teach succinyl attached to the tetrapeptide.

Li and DeJongh each teach N-succinyl peptide derivatives. DeJongh teaches that the terminal amino group is blocked by the reaction with succinic anhydride, and that this product is further derivatized for mass-spec analysis (Abstract). Li teaches that succinylation of peptide hormones led to a decrease in hormone activities (p2638).

It would have been obvious to one of ordinary skill in the art at the time of the invention to succinylate the peptide of '216 for mass spec analysis, as succinlyation of peptides was well known in art. One would have been motivated, with a reasonable expectation of success, to make the succinylated peptide for mass spec analysis, as it

is routine in the analysis of peptides and production of succinylated peptides is known in the art.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1-3, 5-9, 12-19, 22, 23, 25, 26, 28, 30-32, 37, 38, and 118-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over ´216, as applied *supra*, in view of Li and DeJongh, each as applied *supra*, and in further view of U.S. Patent 4,376,765[6] (´765), Köster[7] and WO 91/11457 (´457).

This rejection is in view of the election of species, wherein the claims are drawn to a compound comprising the tetrapeptide βAla-Leu-Ala-Leu, the stabilizer succinyl, the therapeutic agent doxorubicin, and optionally a hydrazide linker. The claims are also drawn to pharmaceutical compositions of the compound, and the tetrapeptide.

The teachings of ´216, Li, and DeJongh are presented *supra*.

´216 teaches the tetrapeptide conjugate βAla-Leu-Ala-Leu-doxorubicin, *supra*, and that the object of the invention is antitumour therapeutic agents (c1:60+). ´216 teaches the compounds as pharmaceutical compositions, specifically saline (c18:17+). ´216 teaches that succinyl group is an alternative to unnatural amino acids (c3:11+).

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[4] Li, et al. J. Biol. Chem. (1960) 235, 2638-2641.
[5] DeJongh, et al. Biomed. Mass Spectrom. (1976) 3, 191-195. abstract.
[6] PTO-1449 P3.
[7] Köster, et al. U.S. 2003/0119021 A1.

´216 teaches βAla and succinyl are stabilizers (c3:7+).´216 does not teach succinylated conjugates. Li and DeJongh each teach succinylated peptides, *supra*.

´765 teaches various succinylated peptides and that the compounds of the invention are of the formula X-Leu-drug, with the stipulation that X is 1-3 amino acids (c2:60+), and that conjugate are stable to blood circulation, dissociate, or cleave in the target cells (or vicinity of), and are able to regenerate the drug in the active form (c1:36+). ´765 teaches BSA-suc-Ala-Leu-Ala-Leu-doxorubicin (c4:66+, Example 1), wherin BSA is linked to the peptide-drug through a succinyl group. ´765 refers to the peptide sequence as a 'spacer arm' (c1:61+) between the drug and the carrier (c2:48+) and that an arm of 4 amino acids in length increased the release of free daunorubicine to a maximal 78 % (c2:53+). ´765 does not teach the elected peptide species, *βAla*-Leu-Ala-Leu.

Because of the breadth of the instant claims ("A compound comprising...") the claims have been interpreted as to allow BSA attached to the 'stabilizer', and is consistent with Applicant's election of succinyl as the stabilizer.

Because Li and DeJongh each teach succinylated peptides, and because the prior art teaches the tetrapeptide *β*Ala-Leu-Ala-Leu linked to the doxorubicin, it is considered an intrinsic property that the compound cleaves as claimed in instant claim 9, and that inclusion of the succinyl group would not alter the intrinsic ability to cleave between Leu-Ala (AA^3-AA^2). Recitation of the target cell and *in vitro/in vivo* activity does not further limit the compound, as the instant claims are drawn to compounds and not to methods. However, because the instant tetrapeptide-drug conjugate has been taught by

the prior art, it is considered an intrinsic property that the compound have the same biological activity, namely cleaving between specific amino acids of the tetrapeptide, and having a specific portion as the active prodrug remaining.

Additionally, Köster teaches that, "[t]hose of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity." (Page 8, column 2 citing, *e.g.*- Watson, *et al. Molecular Biology of the Gene, 4th Edition*, 1987, The Benjamin/Cummings Publishing Company, page 224). In view of the prior art, and in view of the instant specification and drawings (in particular instant Figure 2), absent evidence to the contrary, the essential part of the polypeptide is the Leu-Xaa (AA^3-AA^2) motif, wherein cleavage occurs and amino acids +1 and -1 from the cleavage site, AA^4 and AA^1 respectively, do not alter the intrinsic ability to be cleaved. Further, ´457 teaches that βAla and Ala are both neutral, small, nonpolar amino acids (p20+ and Figure 1) and are deemed to be conservative substitutions based on size, charge, and polarity. Therefore, it is considered a matter of judicious selection and routine optimization to replace AA^4 with any amino acid, particularly a conservative substitution such as *β*Ala for Ala, with the expectation that the compounds would have similar activity, specifically cleaving between AA^3-AA^2.

Furthermore, because of the beneficial teachings of Li and DeJonhgh, with regards to succinylation of peptides, and the teachings of ´765, with regards to using succinylate to link another molecule, such as BSA, to the related tetrapeptide, and the teaching of ´216 that succinyl and βAla are stabilizing groups, it would have been

obvious to one of ordinary skill in the art to use a succinylated peptide to link BSA to the peptide of '216 to make a prodrug which was more soluble and protects the terminal amino group. One would have been motivated, with a reasonable expectation of success, to make the either BSA-suc-βAla-Leu-Ala-Leu-doxorubicin or suc-βAla-Leu-Ala-Leu-doxorubicin, because BSA is taught to be connected to related peptide conjugates through a succinyl group, wherein the peptides differ by a single conservative substitution and have the same function of protecting and delivering doxorubicin. Further, the prior art teaches that succinyl is used to protect terminal amines and is used to link BSA to related peptides which differ by a single conservative substitution and have the same function of protecting and delivering doxorubicin.

It would have been obvious to one of ordinary skill in the art to formulate pharmaceutical compositions of the peptide drugs conjugate, as related compounds having a single conservative amino acid substitution or which are nonsuccinylated are known in the art as prodrugs of doxorubicin. One would be motivated with a reasonable expectation of success to make pharmaceutical compositions of these compounds, as related compounds, with a single conservative amino acid substitution or which are nonsuccinylated, are disclosed in the prior art as prodrug forms of doxorubicin, releasing the active form as indicated in instant Figure 2.

Further, it would have been obvious to one of ordinary skill in the art to make and use the free succinyl-peptide-doxorubicin form as pharmaceutical compositions, as related compounds, tripeptides wherein succinyl is substituted for βAla, and tetrapeptides where succinyl links BSA to related peptides with a single conservative

substitution, are known in the art to be prodrugs, cleaving between the Leu-Ala bond, and have been formulated as saline solutions. As state *supra*, it is deemed a matter of routine optimization and judicious selection to replace Ala with βAla, and that one of ordinary skill in the art would routinely use a conservative substitution of a non-essential amino acid with the expectation that two compounds would act a in similar manner. Additionally, one would have been motivated to make the compounds as pharmaceutical compositions, with a reasonable expectation for success, as related compounds are well known in the art as pharmaceutical compositions, and would be expected to have the same biological activity, cleaving between Leu-Ala and resulting the delivery and release of the active form of doxorubicin.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1-3, 5-19, 22, 23, 25-28, 30-32, 37, 38, and 118-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over ´216 as applied *supra*, in view of ´765, Köster, Li, and DeJongh, each as applied *supra*, in further view of U.S. Patent 6,372,712 B1 (´712) Kaneko, *et al.*[8], Kratz, et al.[9], and Beyer, *et al.*[10]

The instant claims are described *supra*.

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[8] T Kaneko, et al. Bioconjugate Chem. (1991) 2, 133-141.
[9] F Kratz, et al. Arch. Pharm. Pharm. Med. Chem. (1998) 331, 47-53.
[10] U Beyer, et al. J. Med. Chem. (1998) 41, 2701-2708.

The prior art is described *supra*. The prior art does not teach hydrazide as a linker between the tetrapeptide and the doxorubicin.

'712 teaches bifunctional molecules which may be linked covalently or through a linker group (c3:63+), wherein the bifunctional molecule is of the formula Z-L-X, X is a drug moiety, L is a bond or linking group, and Z is a ligand for an endogenous presenter protein (c6:1+). '712 teaches that various linking groups, L, "are known to those of skill in the art and find use in the subject bifunctional molecules" (c17:10+). The linking group hydrazide, is derived from a reactive group, Cbz-hydrazide, as exemplified in Example 2 (scheme at bottom of page and Example 2, c35:30+), wherein hydrazide links compound 1 to the drug, SLF, a non-standard peptide containing compound. Further, Beyer teaches the use of hydrazide to link the anticancer drug chlorambucil to transferrin (2703+), Kratz teaches chlorambucil linked to albumin, and Kaneko teaches alternative binding of doxorubicin to form a hydrazide linkage at the C13 carboxylate.

In view of the beneficial teachings of '712, it would have been obvious to one of ordinary skill in the art to link the peptide to doxorubicin, or a therapeutic compound, with hydrazide, a linker, as doxorubicin is a drug moiety, and the suc-peptide is a ligand for an endogenous presenter protein and '712 teaches that linkers are well known in the art for linking bifunctional molecules, as evidenced by Kratz, Beyer, and Kaneko. One would have been motivated, with a reasonable expectation of success in linking doxorubicin, or any therapeutic compound, to the peptide with a linker group, as '712 teaches that hydrazide is useful in linking a drug moiety to a delivery molecule. In view of the election of the tetrapeptide, the Examiner has concluded that with regards to

cleavage products, it is considered an intrinsic property that if the compound were bound through a hydrazide linkage, it would not cleave the free drug from the leucine residue, nor would AA^2 cleave, as indicated in instant claims 11 and 12, as TOP cleaves between peptides.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

NO CLAIMS ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 8am-430pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571)272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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